REMARKS

The Official Action mailed July 15, 2003, has been carefully studied. The claims in the application are now claims 2-6, 8-17, 20 and 21, and these claims not only define novel and unobvious subject matter under §§102 and 103, but also meet all the requirements of §112, and should be allowed. Applicants therefore respectfully request favorable reconsideration and allowance.

Claims 2-6, 8-17 and 19-24 have been rejected under the first paragraph of §112. This rejection is respectfully traversed.

The rejection states that applicants' specification does not enable the person skilled in the art to practice the invention commensurate in scope with applicants' claims with respect to diagnosing metastasis of malignant tumor to bone using anything other than osteocalcin and bone alkaline phosphatase (BALP), nor does applicants' specification enable the practice of a method of evaluating the therapeutic efficacy of a drug using a marker which reflects osteoblast and osteoclast activity. Respectfully, the literature with which the person skilled in the art is, would be, or should be familiar, is contrary to what the rejection states. In this

regard, please find enclosed copies of the following three document.

1. Miura et al, Endrocrine Journal, 1997, 44(5), pp. 751-757.

2. Maeda et al, The Journal of Urology, February 1997, vol. 157, pp. 539-543.

3. Imai et al, Nihon Hinyoooukigakkai Zassi (Journal of Urological Society of Japan), 89(4), pp 484-491.

Miura shows that there are significant correlations among PYR, DPYR, ICTP and NTx which are bone resorption markers. Please refer to Table 4 of page 755.

Maeda shows that the bone resorption markers DPD and ICTP were highly correlated (r=0.820) and that the bone formation markers ALP and BAP also were highly correlated (r=0.995). In addition, Maeda also shows that the r value between ALP and Oseocalcin (OC) and that between BAP and OC were extremely low, i.e. the former is 0.080 and the latter is 0.075. Please refer to Table 4.

Imai shows that the bone resorption markers D-Pyr (DPD) and ICTP were significantly correlated (r=0.70) and that the bone formation markers ALP and PICP were also significantly correlated (r=0.80). Please refer to the English language abstract (page 484), Fig. 6 (page 489) and Fig. 7 (page 490).

In the light of the teachings mentioned above, it should be clear that the measured values of bone resorption markers in cancer patients with bone metastasis are significantly correlated and that the same applies to bone formation markers except for OC which reflects mineralization. It can be readily concluded that OC is not correlated with another bone formation marker because there is no significant increase in the level of OC in bone metastasis unlike PICP and BALP (please refer to page 5, lines 6-11 of the present specification).

Therefore, applicants submit that the claimed invention absolutely would be enabling for a method of diagnosing metastasis of malignant tumor to bone using a bone resorptive maker other than ICPT which is supported by the working examples as well as using a combination of BALP/OC. What is stated in applicants' specification is not incredible, and is consistent with the literature. In other words, the specification does enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the present invention commensurate in scope with applicants' claims.

In addition, applicants respectfully take the strongest issue with the PTO's comments about applicants' example 3 in the paragraph commencing at about the middle of

page 4 of the Official Action, and it appears that such statements in such paragraph are based on a misunderstanding. In example 3, not only ICTP but also BALP and CA 15-2 were measured. In addition, no conclusion or suggestion is provided in Example 3 to the effect that one marker was sufficient in the evaluation of the therapeutic efficacy of the CAF regimen.

Applicants were able to evaluate the degree of exacerbation of cancer metastasis to bone (PD) by using a bone resorption marker such as ICTP based on the results of Examples 3 and Fig. 4. However, applicants did not monitor amelioration by therapy (CR and IMP). With regard to bone metastasis of a dissolution type, there are no significant increases in the levels of formative markers, namely n=bone formation markers (please refer to page 5, line 4, to page 6, line 1 of applicants' specification).

In addition, in the case of breast cancer in which both bone formation metastasis and bone dissolution metastasis exist, the crossover index value of group NC is close to that of group PD whereas the crossover index value of group CR was not close to that of group IMP (please refer to page 13, lines 2-18 of applicants' specification). Therefore, in order to ensure that the progress of bone metastasis (the degree of aggravation) is diagnosed accurately, not only the evaluation

of formative markers (bone formation markers) but also that of resorptive markers (bone resorption markers) would be necessary.

In other words, in order to understand the pathological condition of metastasis based on various images of bone metastasis obtainable by using bone metabolite markers, both of amelioration by therapy and aggravation of pathological condition must be evaluated. As a result, both the evaluation of bone formation markers and that of bone resorption markers are necessary for accurate diagnosis of metastasis of malignant tumor to bone.

The rejection is unjustified and should be withdrawn. Such is respectfully requested.

Claims 2-6, 8-17 and 19-24 have also been rejected under the second paragraph of §112. This rejection is also respectfully traversed.

First, applicants must respectfully state that applicants' claims are directed to those persons skilled in the present art, and it must be understood that such persons of the present art are very highly skilled. Applicants believe that the claims as previously drafted, particularly considered in light of applicants' specification (fully consistent with the law), would not have been confusing to those highly skilled persons who are skilled in the present

art, and therefore the claims in their previous form are fully in accordance with §112. At worst, claims 6 and 8 in their previous form might be considered objectionable, but only as to form.

Nevertheless, in deference to the examiner's views and to minimize needless argument, a number of cosmetic amendments have been made in claims 6 and 8. These amendments are of a formal nature only, i.e. made to place the claims in better form consistent with U.S. practice or the examiner's understanding of what is necessary or desirable under U.S. practice for the present application. These amendments to claims 6 and 8 are clearly not "narrowing" amendments because the scope of the claims has not been reduced. No limitations have been added these claims, and none are intended.

Applicants submit that the present invention is not all that complex, and it is easily understandable by those skilled in the art by from a consideration of applicants' specification, together with (of course) what is already known in the art and is presumed to be known by those skilled in the art, i.e. the knowledge possessed by those highly skilled persons of the present art. Thus, there are markers of bone formation and markers of bone resorption (page 2 of applicants' specification, Table 1). From the tests reported in example 1 and shown in Fig. 2, those skilled in the present

art will know what to test for, and how to calculate the crossover index. As stated at the bottom of page 10 of applicants' specification:

> It can hence be concluded that the crossover index allows for both diagnosis of the progression of bone metastasis and evaluation of drug efficacy in the treatment of the disease.

The results achieved in example 2 confirm the results of example 1, and are graphically illustrated in Fig. 3. Please consider the conclusions stated at page 12 of applicants' specification, lines 16 *et seq* through the top of page 13.

Example 3 provides additional data. As stated at page 16, lines 18-24, "According to the findings in Examples 1-3, the amelioration of bone metastasis (therapeutic effect) and the degree of its exacerbation can be correctly diagnosed by monitoring two markers, one associated with osteoblasts and targeted to evaluation of therapeutic effect and the other associated with osteoclasts and targeted to evaluation of the worsening of the disease."

As regards claims 16, 17, 20 and 21, the ratios in question have been specified by incorporating the features from claims previously dependent thereon. However, as claims 126, 17, 20 and 21 depend from claim 8 or claim 6, the full scope of these claims is covered by the independent claims 6

and 8. Again, no limitations to applicants' invention are intended; the meaning of the claims remains the same.

Applicants respectfully request withdrawal of the rejection.

As again no prior art has been imposed against any of applicants' claims, the applicants understand that their claims are still deemed by the PTO to define novel and unobvious subject matter §§102 and 103.

Applicants respectfully request favorable reconsideration and allowance.

Respectfully submitted,

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